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| 09/423,712 | 08/25/2000 | Peter Nawroth | 8484-075-999 | 7074 |

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| EXAMINER |
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LI, QIAN J

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| ART UNIT | PAPER NUMBER |
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1632

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/423,712

Applicant(s)

NAWROTH ET AL.

Examiner

Q. Janice Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7-21, 23-28 and 30-35 is/are pending in the application.
- 4a) Of the above claim(s) 18 and 19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-17, 20, 21, 23-28 and 30-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 July 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 20.
- 4) ☒ Interview Summary (PTO-413) Paper No(s). 22.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

The amendment filed April 2, 2003 has been entered and assigned as Paper #21. Claim 29 has been canceled. Claims 7, 20, 30-32 have been amended. Claims 33-35 are newly submitted. Claims 18 and 19 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 7-17, 20, 21, 23-28, and 30-35 are under current examination.

Claim Objections

Claims 7-17, 20, 21, 23-28, 30-35 are objected to because of the claim recitation, "tissue factor", since the term refers to a particular protein, it should be capitalized.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 7-12 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is withdrawn in view of the argument and supporting evidence submitted with Paper #21.

The prior rejection of claims 7-12 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is withdrawn in view of the argument and supporting evidence submitted with Paper #21.

The prior rejection of claims 7-17, and 20-32 under 35 U.S.C. 112, first paragraph, has been modified as following, and the arguments in the previous papers would be addressed to the extent that it applies to the current rejection.

Claims 7-17, 20, 21, 23-28, and 30-35 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for activating blood vessel formation or enhancing wound healing in a subject in need comprising administering a nucleic acid expressing the Tissue Factor (TF) locally, wherein the nucleic acid is a plasmid vector comprising a constitutive promoter, does not reasonably provide enablement for activating blood vessel formation or enhancing wound healing in a subject in need comprising *inducing* local expression of a TF by *any* means or locally administering *any* type of nucleic acid comprising an inducible promoter operably linked to a TF. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Claims are drawn to using any "expressible nucleic acid" for delivering TF. Given the broadest reasonable interpretation, claims encompass using naked DNA, plasmid and viral vectors. The specification only briefly mentioned that the expressible nucleic acid "may be virus or plasmid vectors" (Specification, page 3, line 21), and contemplated several plasmid vectors as suitable vectors for practicing the invention. In the working example, a plasmid vector was used. Therefore, the specification relies on the state of the art as support for use of viral vectors.

In light of the state of the art for using viral vectors in gene therapy, several different vector systems are in use for somatic gene transfer. These include DNA (either naked or complexed), RNA viruses (retroviruses), and DNA viruses (adenovirus, adenoassociated virus, herpesvirus and poxvirus). Each system has perceived advantages and disadvantages, which influence their selection for current or projected

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clinical applications. each type of virus has different host range and tissue tropism and each vector system have different efficiency in transducing different types of cells.

Robbins et al (Pharmacol Ther 1998;80:35-47) teach that each type of vector system has its unique advantages and limitations, "RETROVIRAL VECTORS CAN PERMANENTLY INTEGRATE INTO THE GENOME OF THE INFECTED CELL, BUT REQUIRE MITOTIC CELL DIVISION FOR TRANSDUCTION.

ADENOVIRAL VECTORS CAN EFFICIENTLY DELIVER GENES TO A WIDE VARIETY OF DIVIDING AND NONDIVIDING CELL TYPES, BUT IMMUNE ELIMINATION OF INFECTED CELLS OFTEN LIMITS GENE EXPRESSION IN VIVO. HERPES SIMPLEX VIRUS CAN DELIVER LARGE AMOUNTS OF EXOGENOUS DNA; HOWEVER, CYTOTOXICITY AND MAINTENANCE OF TRANSGENE EXPRESSION REMAIN AS OBSTACLES.

AAV ALSO INFECTS MANY NONDIVIDING AND DIVIDING CELL TYPES, BUT HAS LIMITED DNA CAPACITY"

(abstract). *Robbins et al* go on to teach that non-viral vectors such as naked DNA and liposomes are inefficient in gene transfer to cell nucleus (Section 2, page 36). *Verma et al* (Nature 1997;389:239-42) teach "THE USE OF VIRUSES IS A POWERFUL TECHNIQUE, BECAUSE MANY OF THEM HAVE EVOLVED A SPECIFIC MACHINERY TO DELIVER DNA TO CELLS. HOWEVER, HUMANS HAVE AN IMMUNE SYSTEM TO FIGHT OFF THE VIRUS, AND OUR ATTEMPTS TO DELIVER GENES IN VIRAL VECTORS HAVE BEEN CONFRONTED BY THESE HOST RESPONSE" (last paragraph of left

column on page 239). *Verma et al* teaches particularly regarding to retroviral vector, "A CRITICAL LIMITATION OF RETROVIRAL VECTORS IS THEIR INABILITY TO INFECT NON-DIVIDING CELLS, ... OUR GROUP HAS USED IT TO INFECT MOUSE PRIMARY FIBROBLASTS OR MYOBLASTS WITH RETROVIRAL VECTORS PRODUCING THE FACTOR IX PROTEIN. BUT WITHIN FIVE TO SEVEN DAYS OF TRANSPLANTING THE INFECTED CELLS BACK INTO MICE, EXPRESSION OF FACTOR IX IS SHUT OFF. THIS TRANSCRIPTIONAL SHUT-OFF HAS EVEN BEEN OBSERVED IN MICE LACKING A FUNCTIONAL IMMUNE SYSTEM (NUDE MICE), AND IT CANNOT BE DUE TO CELL LOSS OR GENE DELETION BECAUSE

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THE TRANSPLANTED CELLS CAN BE RECOVERED". (Paragraph bridging left and middle columns of page 240). Therefore, these viral vectors would not be suitable for the instant invention, particularly when a transient expression pattern is desired. Moreover, in paper #15, applicants listed strategies that would enable the instantly claimed invention, including "reducing or even avoiding immune responses against the vector by using *non-viral* vectors" (page 8, lines 4-6). However, the claims are still encompassing using a viral vector. In view of such, the claims do not appear to be enabled in the absence of clarification of the contradictory evidence found in the references and remarks.

Claims 20, 21, 23-28, 33-35 recite a method comprising inducing local expression of a tissue factor nucleic acid in said subject. Given the broadest reasonable interpretation, the recited nucleic acid encompasses both endogenous and exogenous nucleic acids encoding the TF, and claims encompass any means of induction of the TF expression. For example, administering a chemical, which would induce an endogenous TF expression, making a wound that would trigger endogenous TF expression, and administering an agent to activate an inducible promoter in a previously administered exogenous TF plasmid comprising an inducible promoter. These just a few non-limiting examples that a TF could possibly be induced to express locally. The specification contemplated inducing local TF expression by using a genetic vector comprising an inducible promoter, however, the specification fails to teach any other means of induction, thus, fails to provide an enabling disclosure commensurate to the scope of the claims. The same issue was raised in the Office action paper #11, applicants failed to respond to the rejection under 112§ 1st paragraph in paper #15, but did respond to

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the issue raised under 112 § 2nd paragraph and pointing to the paragraph bridging pages 3-4 of the specification as clear support. However, the particular paragraph only briefly mentions using an inducible promoter with regard to inducing local expression, but fails to teach the broadly claimed subject matter, thus, fails to provide an enabling disclosure commensurate with the scope of the claims.

Moreover, although, the specification contemplates using inducible or tissue specific promoters (Specification, paragraph bridging pages 3 and 4), the state of the art was not well developed at the time of instant effective filing date. *Miller et al* (Hum Gene Ther 1997 May;8:803-15) teach that "SOME CIS-REGULATORY SEQUENCES FUNCTION APPROPRIATELY ONLY AFTER INTEGRATION, ... AND CLEARLY WILL FUNCTION BEST IN INTEGRATING VECTORS" (right column, page 805), and "IT IS NOT UNCOMMON THAT CELLULAR C/S-ACTING SEQUENCES (TISSUE SPECIFIC) LOSE SOME OR ALL OF THEIR ABILITY TO RESTRICT EXPRESSION APPROPRIATELY WHEN PLACED IN THE CONTEXT OF A VIRAL VECTOR... THE CELLULAR ENVIRONMENT MAY HAVE A STRONG EFFECT ON PROMOTER ACTIVITY... MANY OF THE PROBLEMS THAT ARE OBSERVED WHEN CELLULAR PROMOTERS ARE PUT IN VIRAL VECTORS ARE DUE TO THE POWERFUL ENDOGENOUS VIRAL TRANSCRIPTIONAL CONTROLS OVERRIDING THE CELLULAR SEQUENCE..." (PAGE 806). The specification fails to teach how to overcome the aforementioned difficulties in the art. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

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For the reasons of record and those set forth above, the instant specification fails to meet the enablement provision set forth under 35 U.S.C. §112, 1st paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The prior rejection of claims 7-10, 13-17, and 20-25 under 35 U.S.C. 102(e) as being anticipated by *McDonald et al* (US 6,120,799), is withdrawn in view of claim amendment and in light of newly submitted evidence indicating the TF induces tissue angiogenesis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The prior rejection of claims 7-17, and 20-27 under 35 U.S.C. 103(a) as being unpatentable over *McDonald et al* (US 6,120,799) as applied to claims 7-10, 13-17, and 20-25 above, and further in view of *Dubensky, Jr. et al* (J Virology 1996 Jan;70:508-19),

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is withdrawn in view of claim amendment and in light of newly submitted evidence indicating the TF induces tissue angiogenesis.

The prior rejection of claims 7-10, 13-17, 20-25, and 28 under 35 U.S.C. 103(a) as being unpatentable over *McDonald et al* (US 6,120,799) as applied to claims 7-10, 13-17, and 20-25 above, and further in view of *Sanford et al* (US 5,100,792), is withdrawn in view of claim amendment and in light of newly submitted evidence indicating the TF induces tissue angiogenesis.

Conclusion

No claim is allowed.

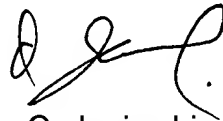
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.


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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Examiner
Art Unit 1632

QJL
June 16, 2003



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